British Journal of Haematology, 1997, **98**, 893–900

The role of compliance as a cause of instability in oral anticoagulant therapy

FELIX J. M. VAN DER MEER,[1] ERNEST BRIËT,[1] JAN P. VANDENBROUCKE,[2] DAGMAR I. ŠRÁMEK,[1] MYRTHE H. P. M. VERSLUIJS[1] AND FRITS R. ROSENDAAL[1,2] *Departments of* [1]*Haematology and* [2]*Clinical Epidemiology, Academic Hospital Leiden, The Netherlands*

Received 7 April 1997; accepted for publication 17 June 1997

Summary. To assess the role of non-compliance as a cause of instability in patients on oral anticoagulant therapy, a follow-up study of stably and instably anticoagulated patients and of patients beginning oral anticoagulant therapy was performed. Compliance was assessed by pill counting and with the use of pill bottles in the cap of which a microprocessor registered the exact date and time of opening of the bottle. (In)stability of oral anticoagulant therapy was expressed as the number of INRs and as the time spent within the target range and by squared sigma. Subsequently, as a pilot study, a randomized intervention study in instable, non-compliant patients was performed in which these patients were or were not informed about the real nature of the cap of the pill bottle.

Nineteen stable and 19 unstable patients and 30 patients beginning therapy were followed for 3 months or less until therapy stopped. Compliance was better in the previously stably anticoagulated patients, although differences were small. Poor compliance was not a major cause of instability in patients starting therapy. Although the pilot intervention study was too small to assess the role of the special pill bottle, it was shown that compliance can be positively affected.

Keywords: compliance, oral anticoagulant therapy, instability, phenprocoumon, thrombosis service.

A number of clinical trials and other investigations have shown the efficacy and relative safety of oral anticoagulant therapy in atrial fibrillation, after myocardial infarction and in patients with a mechanical heart valve prosthesis (Smith *et al*, 1990; EAFT, 1993; ASPECT Research Group, 1994; Atrial Fibrillation Investigators, 1994; Cannegieter *et al*, 1995; Hylek *et al*, 1996), and more information has been gathered about the optimal target ranges, expressed in International Normalized Ratio (INR) (EAFT, 1993; Cannegieter *et al*, 1995; Hylek *et al*, 1996; Rosendaal, 1996). Depending on the indication for therapy a minimal INR of 2·0 or 2·5 is essential for efficacy (Hull *et al*, 1982; Schulman & Lockner, 1985; Cannegieter *et al*, 1995; The European Atrial Fibrillation Trial Study Group, 1995; Rosendaal, 1996). The frequency of bleeding complications, however, rises with INR (Fihn *et al*, 1993, 1996; Van der Meer *et al*, 1993, 1996; Cannegieter *et al*, 1995; The European Atrial Fibrillation Trial Study Group, 1995). Therefore, narrow target zones have been defined at which the anticoagulant effect is aimed. Ideally, to achieve maximum efficacy and minimal bleeding complications all treated patients should be within the target ranges 100% of the time. Reality, however, is different, and generally about 65–75% of INRs are within the target range (Van den Besselaar *et al*, 1988; Cannegieter *et al*, 1995; The European Atrial Fibrillation Trial Study Group, 1995). Various explanations can be offered for this phenomenon: analytical and biological variability of the prothrombin time (Lassen *et al*, 1995), dosage prescription (Fitzmaurice *et al*, 1996), intercurrent diseases, interfering medicaments (Harder & Thürmann, 1996), dietary changes (Paterson & Kwaan, 1986) and, rarely, inherited warfarin resistance (O'Reilly *et al*, 1964).

Poor compliance may also be a cause of instability. In recent years there has been increasing literature on the subject of compliance in various diseases and treatments. Several methods are available to estimate compliance (Urquhart, 1994). The older methods such as interviewing the patient, pill counts and measurements of the drug concentration in plasma all have disadvantages. A recently introduced method is to add a low-dose chemical marker to the tablet (Pullar *et al*, 1988; Kumar, 1989). Low-dose phenobarbital is frequently used as a chemical marker

Correspondence: Dr Felix J. M. van der Meer, Department of Haematology, Academic Hospital Leiden, P.O. Box 9600, 2300 RC Leiden, The Netherlands.

because of its long half-life. Recently, Kumar *et al* (1989) used this method in patients on warfarin therapy, and concluded that poor compliance is a major cause of instability. In our Thrombosis Service the majority of patients use the long-acting coumarin derivative phenprocoumon (Marcoumar®). Theoretically the long half-life should result in a more stable anticoagulant control than with warfarin, because the effect of taking a tablet too many or too few is not so drastic. Nevertheless, we find patients with profound instability. Therefore, either our instable patients are very poor compliers or the idea that long-acting drugs 'smooth out' poor compliance is wrong. Because of the long half-life of phenprocoumon we thought it less informative to add a chemical marker with a long half-life to assess compliance. Another recently introduced method to assess compliance is the use of electronic monitoring devices which register the date and time the pill bottle is opened (Cramer *et al*, 1989). This method is considered to give an accurate reflection of oral drug administration (Urquhart, 1994). Therefore we used this method to study the role of non-compliance as a cause of instability in our patients. Because one cannot be sure that the patient actually took the tablet with the use of this method (only the opening of the bottle is registered) we decided to use this method in combination with pill counts. Furthermore, we assessed the frequency of non-compliance in patients starting oral anticoagulant therapy and performed a small trial to improve compliance.

PATIENTS AND METHODS

The study consisted of three parts. In the first part compliance was assessed and compared in patients who were stably or unstably anticoagulated. In the second part, compliance was assessed in patients starting oral anticoagulant therapy. The purpose of the third part was to assess whether feedback information about poor compliance could be used to improve compliance.

The design of the study was as follows: after informed consent the patients were examined, a short questionnaire was filled out, and a special pill bottle was provided (Medication Event Monitor Systems, Aprex Corporation, Fremont, Calif., U.S.A.). The cap of these bottles contained a microprocessor that registered the exact date and time the bottle was opened. Special equipment and computer software were provided by Aprex to retrieve the data from the cap. The bottle was supplied to the patient with a pre-counted number of tablets amply sufficient for the number of tablets the patient had to take. For this purpose bottles prefilled with 15, 25, 40 or 50 tablets of phenprocoumon were provided by the pharmacy department of the Academic Hospital of Leiden (H. C. R. Brandenburg). The patients were checked at 14 d intervals or more frequently when necessary. During that visit a short history was taken about intercurrent illnesses, changes in co-medication, changes in diet, smoking and alcohol intake, bleeding complications, compliance and events that might have had a serious impact on their lives. Subsequently, the remaining tablets were changed for a fill-up and counted. A blood sample was taken for INR assessment on an Electra 1000C coagulometer (MLA, Pleasantville, New York, U.S.A.) using the Thromborel S reagent (Behringwerke AG, Marburg, Germany). According to the routine procedure in our Thrombosis Service the patient received a dosing list by mail the next day. The patients were not informed about the full purpose of the study. Specifically, they were not informed about pill counting and registration of the time of opening the pill bottle. However, they were told that they were taking part in a study concerning stability of anticoagulant treatment and emphasis was put on the importance of diet, smoking, alcohol intake and stress.

Patient selection

Patients were selected from those treated by the Leiden Thrombosis Service (about 6500 patients). Only patients who were treated for at least 6 months prior to this study with the long-acting coumarin derivative phenprocoumon (Marcoumar®) were eligible. Selection was not based on sex, age, target range or indication for anticoagulant treatment. Stable patients were defined as those who during the previous 6 months had all their INR values within the target range. Unstable patients were defined as those who had at least 50% of their INR values outside the target range during the previous 6 months. Furthermore, the INR values not within the range had to have been both under and above the target range, so as not to include patients who were stably under- or over-anticoagulated. In the first part of the study the patients were followed for 3 months.

The patients for the second part of the study were selected from patients who were newly referred to our Thrombosis Service for anticoagulant therapy. The patients were asked to participate in the study as soon as possible after their first visit, after which the protocol was identical to the first part. Patients were followed for 3 months or less until therapy was stopped.

In the third part of the study, patients were selected from the patients proven unstable in the first two parts. They were followed for 3 months. These patients were randomized in two groups (closed envelope randomization in blocks; block size 2). In group A the patients were informed about the full purpose of the study, the real working mechanism of the cap of the pill bottles, and the counting of tablets. During this part of the study at every check at the Thrombosis Service the result of the pill counting and of the registration of opening the pill bottle was discussed in relation to the patient's own perception and recall and the INR results.

In group B the patients were not informed about the real working mechanism of the cap and the counting of tablets. At every check at the Thrombosis Service they were asked about their compliance, and the importance of good compliance was stressed in relation to the results of INR assessment and (in)stability of the anticoagulant therapy.

All parts of the study were approved by the local Medical Ethics Committee.

Statistics

Calculation of the time within the target range. For the whole observation period the time within the target range was

calculated assuming a change of the INR on the mid-interval between two visits (Van der Meer *et al*, 1993).

Compliance. All data on the exact date and time a pill bottle was opened were registered. For every day it was assessed whether the bottle was opened appropriately or not. Both too many and too few openings were counted as inadequate. Days that no tablets had to be taken were taken into account. The result was expressed as a percentage of the observed openings relative to the required openings.

As a measure of (ir)regularity in opening of the pill-bottle the standard deviation of the time (in minutes) between two openings was calculated. Two (or more) openings within half an hour were counted as one. Days no tablets had to be taken were taken into account. When the bottle was opened on a day that no tablets had to be taken an extra 24 h were added to the opening time. In this way an extra opening was treated equally to a missed opening.

Number of tablets. For each control-interval the number of tablets that had to be taken was assessed. The result of the pill counting was expressed as a percentage of the number of actually taken tablets relative to the number of tablets that had to be taken.

As a measure of (in)stability of the level of anticoagulation the square sigma (σ^2) was calculated (Fihn *et al*, 1993; Cannegieter *et al*, 1996). Sigma was defined as the slope of the change of INR between successive visits, averaged over all visits (Cannegieter *et al*, 1996). The lower the value of σ^2 the more stable was the anticoagulant control.

Statistical analysis of the data was performed with the *t*-test for independent samples with SPSS software.

RESULTS

Patients

As indicated above, the patients were not informed about the real purpose of the study. As a consequence, several interesting observations could be made and some problems in the interpretation of the results arose. Despite our instructions to take the tablets early in the evening, we observed patients who systematically took them in the morning or even during the night (between 1 and 3 a.m.). A patient from the stable group of patients needed to take half a tablet of phenprocoumon per day. It could be deduced that he took out a whole tablet and did not put back the half. As a result, many days were counted as too few openings, even though he most probably took half a tablet a day. Two patients from the unstable group of the first part of the study probably also used another pill delivery system in which the pills were laid out for a whole week. As a result the pill bottle of the study was opened only once a week. One patient in the second part of the study obviously regularly forgot to take a tablet in the evening and took it the next morning. This was counted as two deviations. In the third part of the study one patient of group B (the partially informed group) probably started to use a pill delivery system without informing us.

Part I of the study

Nineteen stable and 19 unstable patients participated in the first part of the study. Patient characteristics are shown in Table I.

The main results are indicated in Table II. During the study period the previously stable patient group remained more stably anticoagulated than the previously unstable group. The mean percentage of INR within the target range was 75 (range 43–100) in the previously stable group in contrast to 51 (range 14–100) in the previously unstable group. The same difference was found when the mean percentage of time within the target range was considered: 75 (range 39–100) for the previously stable group and 52 (range 15–100) for the previously unstable group.

Also, σ^2 as measure of stability showed the most stable anticoagulation in the previously stable patient

Table I. Patient characteristics.

	Part I		Part II	Part III	
	Stable	Unstable		A	B
No. of patients	19	19	30	3	4
Men/women	16/3	16/3	17/13	3/0	3/1
Mean age (range)	61 (46–72)	57 (27–74)	47 (16–74)	46 (27–64)	61 (42–71)
Target range*	M: 18	M: 13	L:13	M:2	M:3
	H: 1	H: 6	M:17	H:1	H:1
Indication for anticoagulant therapy					
Arterial thrombotic disease	17	10	9	2	1
Atrial fibrillation	1	2	7	–	1
Heart valve prosthesis	1	6	1	1	1
Venous thromboembolism†	–	1	13	–	1

* L (low) = INR 2·5–3·0–3·5; M (median) = INR 3·0–3·5–4·5; H (high) = INR 3·5–4·0–4·8.
† Prophylaxis and treatment.

Table II. Results.

	Part I			Part II	Part III	
	Stable (mean (range))	Unstable (mean (range))	*P*	Mean (range)	A (mean (range))	B (mean (range))
Percentage INR in target range	75 (43–100)	51 (14–100)	0·001	50 (0–100)	69 (50–86)	66 (43–86)
Percentage time in target range	75 (39–100)	52 (15–100)	0·002	49 (0–100)	72 (54–93)	66 (39–90)
Opening of pill box*						
Percentage good	88·2 (56–99)	81·4 (15–100)	0·31	92·8 (57–100)	86·3 (78–92)	72·3 (43–97)
Percentage too many	3·7 (0–14)	4·3 (0–32)	0·76	3·7 (0–19)	4·3 (1–6)	10·8 (1–35)
Percentage too few	8·1 (0–39)	14·3 (0–84)	0·34	3·5 (0–29)	9·7 (5–17)	17 (1–56)
SD of opening time†	513 (206–1590)	947 (195–3807)	0·17	380 (174–952)	603 (373–992)	1043 (173–2701)
No. of pills taken (%)‡	99 (76–109)	102 (91–134)	0·23	98 (76–109)	99 (97–102)	103 (81–132)
Stability (σ^2)	0·402 (0·017–1·2)	1·248 (0·058–3·329)	0·004	0·903 (0·031 - 4·576)	1·737 (0·189–4·04)	0·8667 (0·094–1·853)

* Percentage of observed openings of the pill bottle relative to the required openings.
† Standard deviation of the time (in minutes) between two openings of the pill bottle.
‡ Percentage of the number of tablets that was actually taken relative to the number that had to be taken.

group: 0·402 (range 0·017–1·2) versus 1·248 (range 0·058–3·329) in the previously unstable patient group.

Considering the opening of the pill bottle, the mean percentage of 'good' opening in the previously stable patient group was 88·2 (range 56–99) in contrast to 81·4 (range 15–100) in the previously unstable group. Both in the previously stable, as in the previously unstable patient group, the pill bottle was opened too few times (mean percentage 8·1 (range 0–39) and 14·3 (range 0–84)), rather than too many times (mean percentage 3·7 (range 0–14) and 4·3 (range 0–32)).

The variability of the time that the pill bottle was opened was expressed by the standard deviation of the time between openings. In the previously stable patient group the mean standard deviation was 513 min (range 206–1590) in comparison to 947 min (range 195–3807) in the previously unstable group.

In the previously stable patient group the mean percentage of the number of pills that had been taken in relation to the number that had to be taken was 99 (range 76–109) in comparison to 104 (range 92–136) in the previously unstable group.

In Fig 1 the percentage of time within the target zone in relation to the percentage of 'good' opening of the pill bottle is shown, both for the stable and the unstable patient group.

In Table II it can be seen that the differences between the previously stable and unstable group were statistically significant for the percentage INR and the percentage time within the target range and for the σ^2. For the other parameters the differences were not significant.

Part II of the study

Thirty patients starting oral anticoagulant therapy participated in the second part of the study. Patient characteristics are shown in Table I and the main results in Table II. The mean percentage of INR was 50 (range 0–100) and of time within the target range was 49 (range 0–100). In this group the mean σ^2 as a measure of stability was 0·903 (range 0·031–4·576). The mean percentage of 'good' opening of the pill bottle was 92·8 (range 57–100). In this group the mean percentage of opening the pill bottle too many times was 3·7 (range 0–19), the same as the mean percentage of opening too few times: 3·5 (range 0–29). The mean standard deviation of the time between openings of the pill bottle was 380 min (range 174–952). The mean percentage of the number of pills taken adequately was 98 (range 76–109).

As can be seen in Fig 2, 24/30 patients (80%) opened the pill bottle on the right day >90% of the time. Even among these 24 near-perfect compliers, only eight (33%) had their INR within the target range for >70% of the time. Only half (13/24) of them had their INR within the target range for >50% of the time.

Part III of the study

Seven patients participated in the third part of the study. These patients were randomized between group A 'fully informed' (three patients) and B 'partially informed' (four patients). The characteristics of the patients are shown in

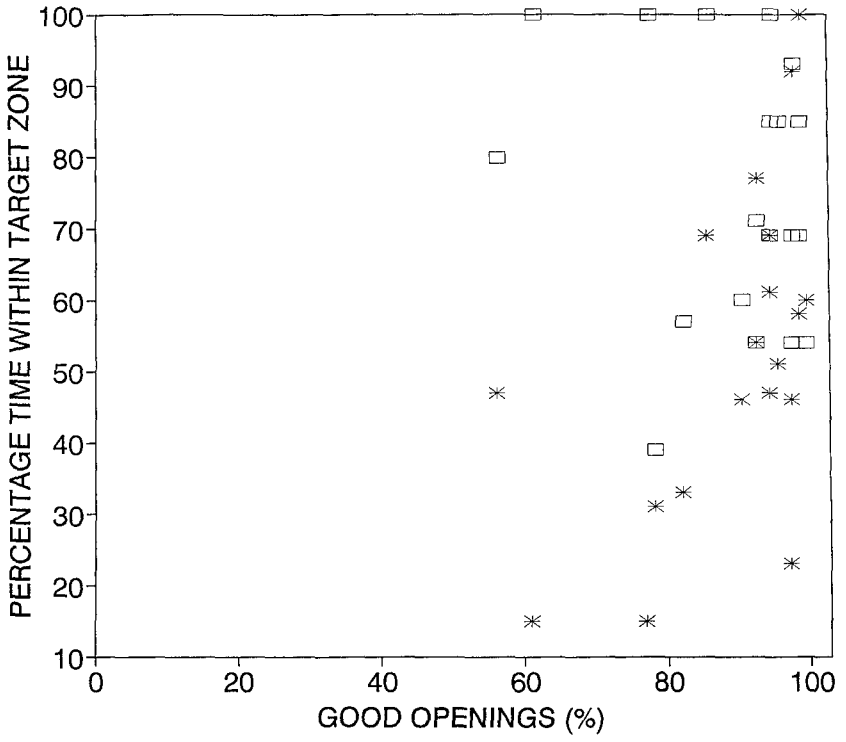

Fig 1 Percentage time within the target zone in relation to the percentage of good opening of the pill bottle in the first group of patients (□) stable patients (*) unstable patients

Table I and the results in Table II The mean percentage of INR within the target range was similar in the two groups (69% range 50–86% in group A and 66% range 43–86% in group B) The mean percentage of time within the target range was slightly higher in group A (72% range 54–93) than in group B (66% range 39–90%) The mean percentage of opening the pill bottle adequately in group A was 86 3 (range 78–92) in comparison to 72 3 (range 43–97) in group B In both groups the bottle was opened too few times rather than too many times The mean standard

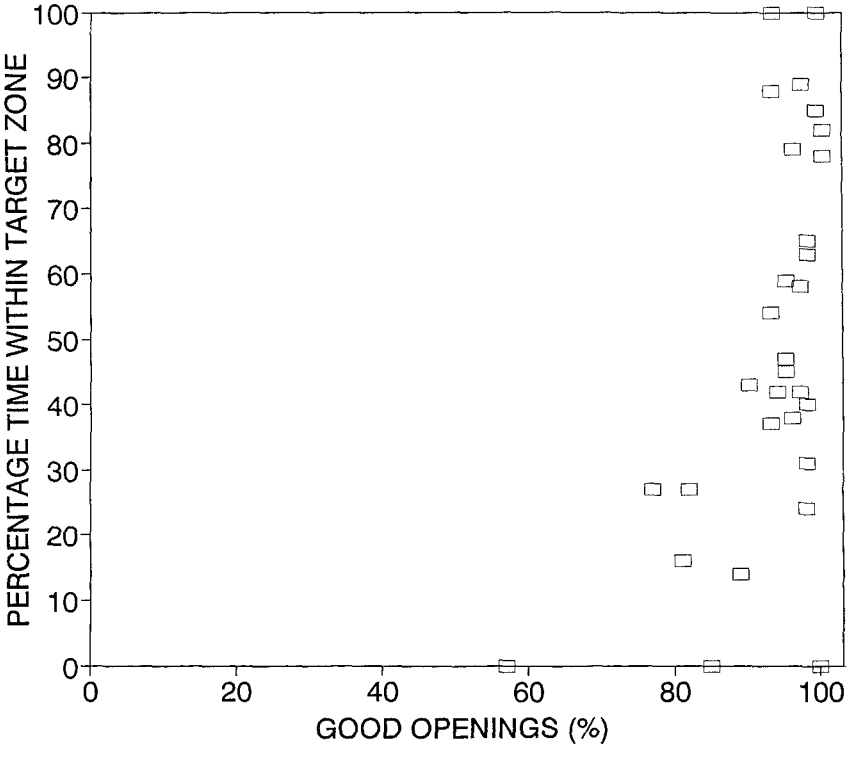

Fig 2 Percentage time within the target zone in relation to the percentage of good opening of the pill bottle in the second group of patients (starting oral anticoagulant therapy)

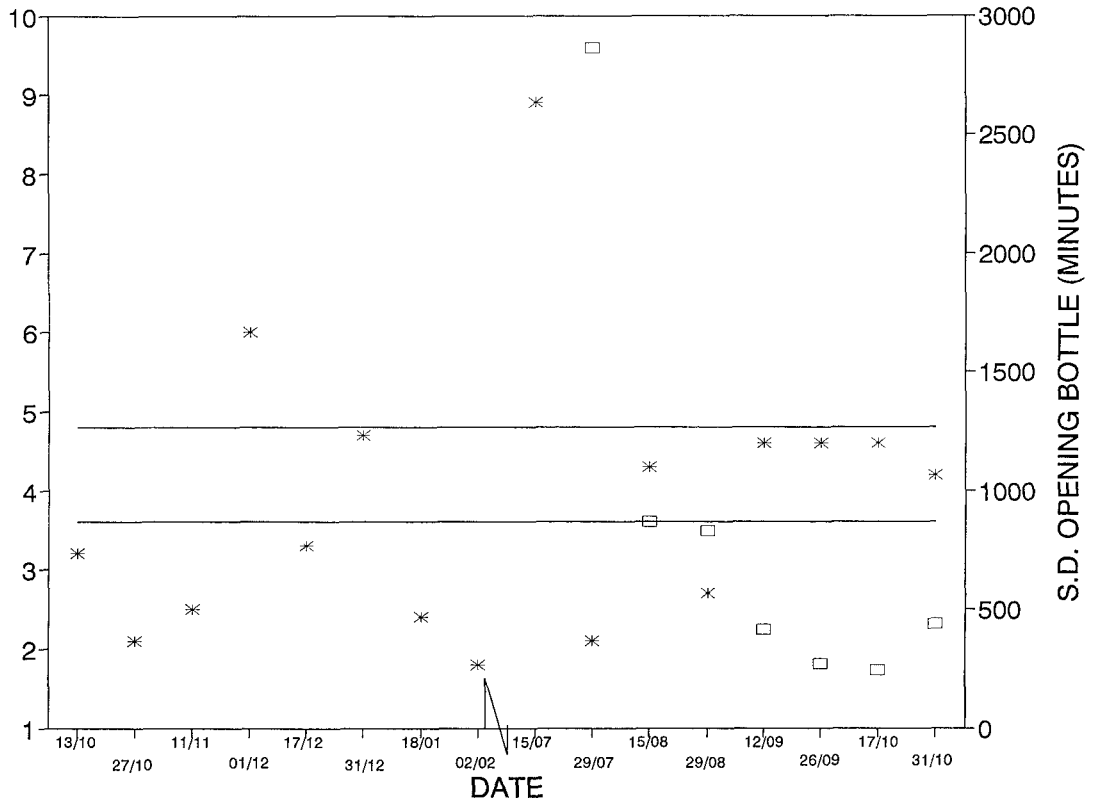

Fig 3. INRs (*) and standard deviation of the opening of the pill bottle in minutes (□) for the patient of the case history.

deviation of the time between bottle openings was lower in group A (603, range 373–992) than in group B (1043, range 173–2701). There was no difference in the mean percentage of the number of pills taken: group A 99%, range 97–102%; group B 103%, range 81–132%. Mean σ^2 was lower in group B (0·8667, range 0·094–1·853) than in group A (1·737, range 0·189–4·04).

Illustrative case history of a remarkable patient

A 27-year-old man, well known to our Thrombosis Service because of his supposed poor compliance, used oral anticoagulants because of prosthetic heart valve implantation in 1992 (Carbomedics, in mitral and in aortic position). He was known to abuse alcohol, and have psychological and social problems; he smoked but did not use drugs. His anticoagulant control was invariably bad, with INR values varying from 2·1 to 9·1, and seldom within the target range, but he did attend the clinic at regular intervals. The prescribed dose of phenprocoumon also varied largely because of his instability and poor compliance: between a mean daily dose of 0·85 and 1·40 tablets. During the first part of the study his control remained poor. There was a large variation of INR values (from 1·8 to 6·0; Fig 3). Frequently, he forgot to take his tablets from the special study pill bottle and he forgot to take the bottle back to the Thrombosis Service. So in the first part of the study it was virtually impossible to evaluate the number of tablets he took and the times he opened the bottle. Despite this he was motivated to improve his behaviour and he agreed in participation in the third part of the study. He was randomized to group A, so he was fully informed about the purpose of the study and the nature of the special pill bottle. Discussing his compliance in relation to the achieved INRs and informing him repeatedly about the need for good anticoagulant control and the inefficacy and dangers of bad control improved his compliance considerably. In the first 8 weeks of the third part of the study he did not take his tablets from the study bottle in 16/59 days, whereas in the last 47 days he only missed 2 days. The percentage of tablets he took improved from 88% to 100%. The standard deviation of the time between openings of the pill bottle shortened considerably (Fig 3). In contrast to the first 8 weeks, his INR was, in the last 47 days, always within the target range (Fig 3). This case history shows that it is possible to improve compliance by giving extra attention and information to the patient. However, the extra value of the special pill bottle to help the feedback cannot be deduced from a single case.

DISCUSSION

The results of part I of the study indicate that the method we used is effective in assessing compliance in patients on oral anticoagulant therapy. Patients who were stably anticoagulated prior to our study remained more stably anticoagulated during the study period in comparison to the

previously unstable group. The previously stable patients opened the pill bottle more often on the prescribed day, indicating a better compliance, although the difference was not statistically significant. The variability of the opening times of the pill bottle was also less in these patients. The mean percentage of tablets taken in the two groups, however, did not differ materially (94% and 104%), which indicates that pill counts are an insensitive method to assess compliance in this setting.

We started this study with the hypothesis that poor compliance was an important cause of instability. Although we found some differences in compliance between the previously stable patient group and the previously unstable group, this was much less than we had expected. Therefore although poor compliance contributes to instability, it clearly is not the only, and possibly a minor, factor.

Patients starting oral anticoagulant therapy were analysed in part II of the study. It can be deduced both from Table II and Fig 2 that as a group these patients took their tablets regularly and as prescribed. In fact their compliance was better than the compliance of the stable patients of part I. Despite their good compliance, many patients were not adequately anticoagulated. Although inadequate anticoagulation is frequent among starters, poor compliance clearly is not a major cause of the instability. Probably, correct dose determination is a major contributor to instability in these patients.

In part III of the study we evaluated whether it was possible to improve compliance and we assessed the possible role of the special pill bottle in this regard. The number of patients in our study was small and the study should be interpretated as a pilot study. From Table II and the case history it appears that compliance can be improved by special attention and devices. The patients were checked more frequently and were seen separately by one of the investigators. The extra attention, together with the extra information on the value of stable anticoagulant therapy and the risks of instability, played a major role in their improvement. The additive value of the special pill bottle to this improvement is difficult to assess. Further studies are necessary in this regard.

The purpose of our study was to assess the frequency of poor compliance and the role of poor compliance as a cause of unstable anticoagulant control. Therefore we decided not to tell the patients about the background of the study and the real purpose of the special pill bottles. Informing the patients would probably have resulted in a change of behaviour and compliance; this study would then be seen as a behavourial scientific sociological rather than a medical experiment. In behavourial sociological sciences it is accepted that, when desirable, participants are not fully informed. Our local Medical Ethics Committee agreed with the procedure as described after a small adjustment of the original protocol. The original plan was to give the patients another explanation for the special pill bottles; this was changed, however, to giving no explanation at all and leaving the matter of the pill bottle unmentioned. When a few patients persistently asked about the bottles we admitted that the bottles were designed to measure compliance. After the study was completed and analysed all patients were informed about the real nature of the study and the pill bottles. In the same letter the patient's own results were given. Not one patient reacted negatively about not being informed; we feel this is a justification of our approach.

As a result of not giving full information a number of problems arose which made the interpretation of the results more difficult. Nevertheless, the results of our study provide valuable information on the role of compliance in the stability of patients on oral anticoagulant therapy.

ACKNOWLEDGMENT

This study was supported by grant 93.001 of the Trombose Stichting Nederland.

REFERENCES

Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group (1994) Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet*, **343**, 499–503.

Atrial Fibrillation Investigators (1994) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Archives of Internal Medicine*, **154**, 1449–1457.

Cannegieter, S.C., Rosendaal, F.R., Bollen, W.L.E.M. & Briët, E. (1996) Risk factors for ischemic and hemorrhagic stroke in the anticoagulant treatment of patients with mechanical heart valve prostheses. In: Optimal oral anticoagulant therapy in patients with mechanical heart valves (Thesis).

Cannegieter, S.C., Rosendaal, F.R., Wintzen, A.R., Van der Meer, F.J.M., Vandenbroucke, J.P. & Briët, E. (1995) Optimal oral anticoagulant therapy in patients with mechanical heart valves. *New England Journal of Medicine*, **333**, 11–17.

Cramer, J.A., Mattson, R.H., Prevey, M.L., Scheyer, R.D. & Ouelette, V.L. (1989) How often is medication taken as prescribed? A novel assessment technique. *Journal of the American Medical Association*, **261**, 3273–3277.

EAFT (European Atrial Fibrillation Trial) Study Group (1993) Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*, **342**, 1255–1262.

Fihn, S.D., Callahan, C.M., Martin, D.C., McDonell, M.B., Henikoff, J.G. & White, R.H. (1996) The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Annals of Internal Medicine*, **124**, 970–979.

Fihn, S.D., McDonell, M., Martin, D., Henikoff, J., Vermes, D., Kent, D. & White, R.H. (1993) Risk factors for complications of chronic anticoagulation. *Annals of Internal Medicine*, **118**, 511–520.

Fitzmaurice, D.A., Hobbs, F.D.R. & Murray, J.A. (1996) Monitoring oral anticoagulation in primary care: quality assurance and computerised decision support will help to minimise inconsistensies. *British Medical Journal*, **312**, 1431–1432.

Harder, S. & Thürmann, P. (1996) Clinically important drug interactions with anticoagulants: an update. *Clinical Pharmacokinetics*, **30**, 416–444.

Hull, R., Hirsh, J., Jay, R., Carter, C., England, C., Gent, M., Turpie, A.G.G., McLouglin, D., Dodd, P., Thomas, M., Raskob, G. & Ockelford, P. (1982) Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *New England Journal of Medicine*, **307**, 1676–1681.

Hylek, E.M., Skates, S.J., Sheehan, M.A. & Singer, D.E. (1996) An analysis of the lowest effective intensity of prophylactic

anticoagulation for patients with nonrheumatic atrial fibrillation *New England Journal of Medicine*, **335**, 540–546

Kumar, S., Haigh, J R M., Rhodes, L E., Peaker, S., Davies, J A., Roberts, B E & Feely, M P (1989) Poor compliance is a major factor in unstable outpatient control of anticoagulant therapy *Thrombosis and Haemostasis*, **62**, 729–732

Lassen, J F., Brandslund, I & Antonsen, S (1995) International normalized ratio for prothrombin times in patients taking oral anticoagulants critical difference and probability of significant change in consecutive measurements *Clinical Chemistry*, **41**, 444–447

O'Reilly, R A., Aggeler, P M., Silvija Hoag, M., Leong L S & Kropatkin, M L (1964) Hereditary transmission of exceptional resistance to coumarin anticoagulant drugs *New England Journal of Medicine*, **271**, 809–815

Paterson, P E & Kwaan, H C (1986) Current concepts of warfarin therapy *Archives of Internal Medicine*, **146**, 581–584

Pullar, T., Birtwell, A J., Wiles, P G., Hay, A & Feely, M P (1988) Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice, or three times daily *Clinical and Pharmacological Therapeutics*, **44**, 540–545

Rosendaal, F.R (1996) The Scylla and Charybdis of oral anticoagulant treatment *New England Journal of Medicine*, **335**, 587–589

Schulman, S & Lockner, D. (1985) Relationship between thromboembolic complications and intensity of treatment during long-term prophylaxis with oral anticoagulants following DVT *Thrombosis and Haemostasis*, **53**, 137–140

Smith, P., Arnesen, H & Holme, I (1990) The effect of warfarin on mortality and reinfarction after myocardial infarction *New England Journal of Medicine*, **323**, 147–152

The European Atrial Fibrillation Trial Study Group (1995) Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia *New England Journal of Medicine*, **333**, 5–10

Urquhart, J (1994) Role of patient compliance in clinical pharmacokinetics a review of recent research *Clinical Pharmacokinetics*, **27**, 202–215

Van den Besselaar, A M H P, Van der Meer, F J M & Gerrits-Drabbe, C W (1988) Therapeutic control of oral anticoagulant treatment in the Netherlands *American Journal of Clinical Pathology*, **90**, 685–690

Van der Meer, F J M., Rosendaal, F R., Vandenbroucke, J P & Briet, E (1993) Bleeding complications in oral anticoagulant therapy an analysis of risk factors *Archives of Internal Medicine*, **153**, 1557–1562

Van der Meer, F.J M., Rosendaal, F.R., Vandenbroucke, J P & Briet, E (1996) Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. *Thrombosis and Haemostasis*, **76**, 12–16